# A double blind placebo controlled study of early and late administration of recombinant tissue plasminogen activator in acute myocardial infarction

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SUMMARY  Within four hours of the onset of acute myocardial infarction 57 consecutive patients were randomised blindly to infusion of 150 mg recombinant tissue plasminogen activator (rt-PA) (group 1) over five hours or placebo (group 2) when they were first seen outside hospital or in the accident and emergency department. When they were admitted to the coronary care unit patients in group 1 also had placebo infused and those in group 2 were treated with rt-PA as well as placebo. Treatment with rt-PA started at a mean of 119 minutes (range 38–235) after the onset of pain in group 1 and 187 minutes (range 80–285) after the onset of pain in group 2. In 19 (79%) of 24 in group 1 and 16 of 25 (64%) in group 2 cardiac catheterisation 10–14 days after infarction showed thrombolysis in myocardial infarction grades 2 or 3. There was a mean percentage shortening of the infarct related segments (Leighton method) of 16% in group 1 and 10·3% in group 2. For patients with anterior infarction mean percentage shortening was 20·5% in group 1 and 12·2% in group 2. Although there was no significant difference in global ejection fraction as assessed by contrast ventriculography or radionuclide ventriculography the infarct related regional third ejection fraction (a measure of the function of the territory of the affected coronary artery) was significantly improved by early treatment (41% group 1 and 28% group 2). Assessment of infarct size by the QRS scoring method of Palmeri showed QRS score $\leqslant 3$ in 15/25 patients in group 1 and 8/27 in group 2. Nine patients developed 11 episodes of ventricular fibrillation; all patients in whom ventricular fibrillation developed during treatment with rt-PA were successfully resuscitated. There was no clinically significant bleeding. In seven (12%) patients clinical and electrocardiographic criteria suggested reocclusion. Five patients died from cardiac causes.

Prehospital administration of rt-PA was feasible and significantly reduced the delay before thrombolysis was started. Earlier treatment improved myocardial function in the infarct area and reduced the infarct size.

Recombinant tissue plasminogen activator (rt-PA) used in the acute phase of myocardial infarction is an effective thrombolytic agent that improves left ventricular function after clot lysis.[1][2] In dogs the metabolic changes induced by ischaemia increased with time from the onset of experimental occlusion of a coronary artery.[3] It follows that earlier lysis of an occluding thrombus in the coronary artery of a patient with evolving acute myocardial infarction should further limit myocardial damage and reduce infarct size, and thus improve left ventricular function. To test this hypothesis we performed a double blind placebo controlled study to compare early and late administration of rt-PA to patients in whom treatment started within four hours of the onset of acute myocardial infarction.

## Patients and methods

Patients with suspected acute myocardial infarction seen outside hospital by staff on the mobile coronary care unit or in the accident and emergency depart-

ment of the hospital were considered for entry into the study. All were aged less than 75 years, had had chest pain lasting less than four hours, and had ST segment elevation of 1 mm in at least two standard leads or in two precordial leads of the electrocardiogram. We excluded women of childbearing age; patients with previous cerebrovascular stroke, a history of generalised bleeding diathesis, or recent trauma or operation; or left bundle branch block on the electrocardiogram.

Continuous electrocardiographic monitoring was started, an intravenous cannula was put in place, and diamorphine was given for pain relief. rt-PA (double chain) and placebo for each patient were supplied by Wellcome research laboratories in pre-packed cartons that were used in sequence. When patients became pain free they were randomised blindly to receive rt-PA (group 1) or placebo (group 2). Allocation depended on whether the first colour coded section of the carton contained placebo or active agent. The contents of the vials from this section were dissolved and infused intravenously (fig 1). Patients then proceeded directly to the coronary care unit where the contents from the second section of the same carton were dissolved and infused, via a line in the contralateral arm, concurrently and at the same rate as the first infusion. Thus patients in group 1 started treatment with rt-PA before admission to the coronary care unit whereas those in group 2 started rt-PA after admission to the coronary care unit. rt-PA (100 or 115 mg) was infused intravenously over 90 minutes and 50 or 35 mg respectively was infused over the next three and a half hours. Intravenous heparin (1000 units/h) was started at the end of the first infusion. Battery powered infusion pumps (Graseby MS 2000 and Graseby MS 16A) were used to deliver rt-PA, placebo, and heparin at the desired rate.
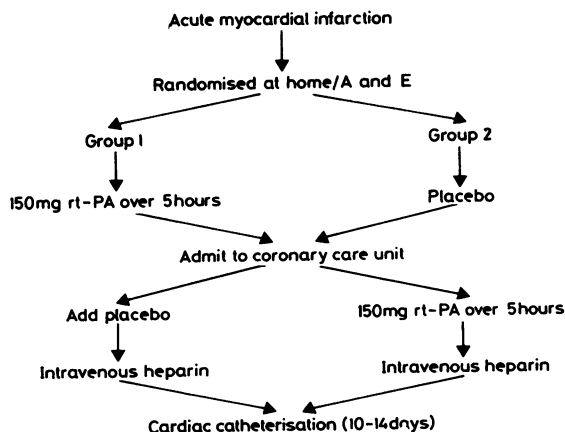
Patients had standard coronary care including continuous electrocardiographic monitoring before and during admission to the coronary care unit. Throughout their hospital stay, bleeding and other complications were noted.

Infarct size was assessed by the QRS scoring method of Palmeri *et al*.[4] Electrocardiograms recorded 48–72 hours after infarction were assessed by an investigator who was unaware of the treatment group. Cardiac catheterisation was performed by the Judkins technique at 10–14 days after infarction or earlier if clinically indicated. Contrast ventriculography was performed in the right anterior oblique 30° view and selective coronary angiography was carried out. The global ejection fraction was calculated according to Dodge's area/length method, and regional wall movement in the infarct area was assessed by Leighton's method.[5] Segments 2 and 3 were used to assess anterior infarction and 7 and 8 for inferior infarction (figs 2–4). Coronary angiograms were scored by the thrombolysis in myocardial infarction (TIMI) grades (0–3).[6] All angiograms and ventriculograms were assessed by experienced investigators who were unaware of the treatment group. Gated blood pool scanning was performed whenever possible during hospital admission or soon after discharge. Global ejection fraction and infarct related regional third ejection fraction (used as a measure of function in the area of infarction) were calculated by an investigator who was unaware of the patient's treatment group. Gated blood pool scanning was performed with an Ohio-Nuclear Sigma 420 Gamma Camera interfaced to an MCS-560 Nuclear Medicine Computer for acquisition and processing data. Global ejection fraction was
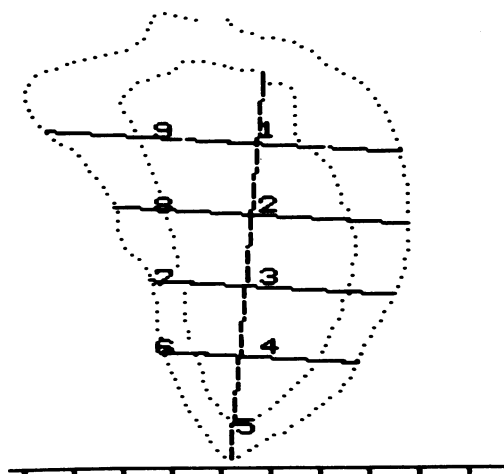


Fig 1  *Plan of the study.*



Fig 2  *Computer printout of a normal left ventriculogram assessed by the Leighton method.*

measured in the standard way. After calculation of global ejection fraction the infarct related regional third ejection fraction was calculated for each of the thirds of the ventricle subtended by the three main coronary arteries. Thus the inferoapical ejection fraction was used as a measure of function of the territory of the right coronary artery, the anteroseptal for the left anterior descending, and posterolateral for the circumflex coronary artery. Infarct related regional third ejection fraction was calculated by standard software incorporated in the system. The program defined the centre of the left ventricular image in diastole and then defined three sectors of 120° that correspond to the area of the left ventricle subtended by each of the three coronary arteries.

Univariate methods of analysis are used throughout the paper. For assessment of time to onset of treatment, global and infarct related regional third ejection fraction, and regional wall movement we used Student's $t$ test for unpaired data. QRS scores were assessed by the $\chi^2$ test.

We obtained the approval of the research ethical committee of the Faculty of Medicine, Queen's University of Belfast before we started the study.

## Results

Fifty seven consecutive patients (47 men, 10 women) mean age 58 years (37–74 years) were studied. Forty nine patients were first seen by staff in the mobile coronary care unit and eight were seen in the accident and emergency department. Twenty seven patients entered group 1 and 30 group 2. There was no significant difference in infarct distribution or previous history of infarction (table 1). Infusion of rt-



NAME:
DATE:  27.4.87
HR  = 70.0    BSA= 1.94
EDV= 101.9 ML/M2
ESV=  47.7
SV  =  54.2
EF= 0.53    CI= 3.8
WT  = 0.86 CM
WMI= 111.5 GM/M2

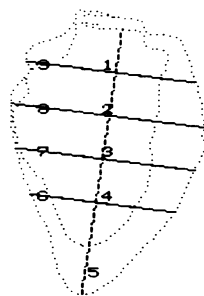|   | % | NORM |
|---|---|------|
| 1 | 42 |   | 41–65 |
| 2 | 49 |   | 41–69 |
| 3 | 47 |   | 38–66 |
| 4 | 49 |   | 43–71 |
| 5 | 53 |   | 23–61 |
| 6 | 26 | L | 44–66 |
| 7 | 5 | L | 33–49 |
| 8 | 7 | L | 28–41 |
| 9 | 27 |   | 8–34 |

Fig 3  Leighton assessment of a ventriculogram from a patient with inferior infarction. Hypokinesis was greatest in segments 7 and 8. HR, heart rate; BSA, body surface area; EDV, end diastolic volume; ESV, end systolic volume; SV, stroke volume; EF, ejection fraction; CI, cardiac index; WT, wall thickness; WMI, wall mass index; L, hypokinetic segment.



NAME:
DATE:  18.5.87
HR  = 70.0    BSA= 1.74
EDV=  66.3 ML/M2
ESV=  43.9
SV  =  22.4
EF= 0.34    CI= 1.6
WT  = 0.77 CM
WMI=  79.1 GM/M2

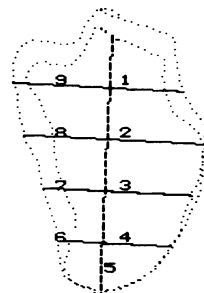|   | % | NORM |
|---|---|------|
| 1 | 23 | L | 41–65 |
| 2 | 4 | L | 41–69 |
| 3 | -6 | L | 38–66 |
| 4 | -3 | L | 43–71 |
| 5 | -6 | L | 23–61 |
| 6 | 33 | L | 44–66 |
| 7 | 34 |   | 33–49 |
| 8 | 34 |   | 28–41 |
| 9 | 15 |   | 8–34 |

Fig 4  Leighton assessment of a ventriculogram from a patient with anterior infarction. See legend to fig 3 for abbreviations.

PA was started a mean of 119 minutes (range 38–235) after the onset of pain in group 1 and after a mean of 187 minutes in group 2 (range 80–285) (p = 0·0005, 95% confidence interval 35 to 101) (table 2).

Reperfusion was assessed from coronary angiograms performed a mean of 10·7 days after infarction in group 1 and 11·5 days after infarction in group 2. TIMI grade 2 or 3 thrombolysis was seen in 19/24 (79%) of assessable coronary angiograms in group 1 and 16/25 (64%) in group 2. Five patients died before angiography, one patient had a reinfarction and was given a second dose of rt-PA before angiography, and in two patients disease was so severe in all three vessels that the infarct related artery could not be identified with certainty.

There was no difference in mean global ejection fraction between the two groups (table 3). Table 4 shows the percentage shortening of the infarct related segments as assessed by the Leighton method. The difference in mean percentage shortening between the two groups is just outside the conventional 95% level of significance (16% $v$ 10·3%, p = 0·06, 95% confidence interval −1·6 to 13). However, for patients with anterior myocardial infarction the mean (SEM) percentage shortening was significantly bet-

Table 1  Infarct distribution and previous history of myocardial infarction (MI)

|   | Group 1 27 patients | Group 2 30 patients |
|---|---|---|
| Infarct: | | |
| Anterior | 13 | 18 |
| Inferior | 14 | 11 |
| Lateral | 0 | 1 |
| Previous MI: | | |
| 0 | 22 | 24 |
| 1 | 3 | 5 |
| 2 | 1 | 0 |
| >2 | 1 | 1 |

Table 2   *Time to start of first and second infusion for groups 1 and 2*

|  | Mean time to 1st infusion (min) | Mean time to 2nd infusion (min) |
|---|---|---|
| Group 1 | rt-PA 119* | Placebo 169 |
| Group 2 | Placebo 129 | rt-PA 187* |

*p = 0.0005.

Table 4   *Mean (SEM) percentage shortening of the infarct related segments as assessed by the Leighton method*

| Infarct site | Treatment group | | p |
|---|---|---|---|
|  | Group 1 | Group 2 |  |
| All sites | 16·0  (2·72) | 10·3  (2·56) | 0·06 |
| Anterior | 20·5  (2·99) | 12·2  (2·23) | 0·01 |
| Inferior | 10·7  (4·58) | 7·7  (5·26) | 0·34 |

ter for those treated early (20·5 (2·99)%) than for those treated late (12·2 (2·23)%) (p = 0·01, 95% confidence interval 0·9 to 15·7).

There was no significant difference between the two groups when the global ejection fraction was assessed by radionuclide ventriculography (table 5). However, the infarct related regional third ejection fraction was significantly better for patients in group 1 (41%) than in group 2 (28%) (p < 0·05, 95% confidence interval −0·8 to 26·8) (one tailed $t$ test).

The QRS scoring method of Palmeri *et al* showed that 15/25 patients from group 1 had a QRS score $\leqslant 3$ compared with 8/27 from group 2 ($\chi^2$ = 4·84, p < 0·05). Of the remaining five patients one had Wolff-Parkinson-White syndrome, one right bundle branch block, and three died before the 48–72 hour electrocardiogram was performed.

Nine patients developed 11 episodes of ventricular fibrillation—four patients from group 1 and five from group 2. Of the 11 episodes, seven occurred during treatment with rt-PA, one occurred during placebo, and three occurred after rt-PA infusion (one on day 2 and one on day 5 after infarction and one on day 7 during reinfarction). There were three episodes of ventricular fibrillation during treatment with rt-PA before admission to the coronary care unit and in all three cases resuscitation was successful. Seven of the nine patients with ventricular fibrillation were initially resuscitated and six survived to leave hospital.

In 27 patients there was minor cutaneous bruising at sites of venepuncture or catheterisation or both. One patient developed a bloody ooze from a recent tooth extraction site, one had coffee ground vomit, and two had haematuria (soon after bladder catheterisation in one). No patient required transfusion.

In seven (12%) patients (three in group 1 and four in group 2) clinical and electrocardiographic criteria suggested reocclusion. One of these received a

Table 3   *Left ventricular angiography.*

|  | Mean global ejection fraction (%) | |
|---|---|---|
|  | Group 1 | Group 2 |
| All infarcts | 50 | 48 |
| Anterior | 49 (n = 13) | 44 (n = 15) |
| Inferior | 51 (n = 11) | 55 (n = 11) |

second dose of rt-PA with successful reperfusion.

Five patients died from cardiac causes: three from cardiogenic shock, one from mesenteric embolisation complicating left ventricular mural thrombus and cardiogenic shock, and one from asystole after ventricular fibrillation. Two of the deaths were in group 1 and three were in group 2.

## Discussion

Myocardial damage spreads as a wave front from endocardium to epicardium after occlusion of the infarct related coronary artery. Reducing the delay before lysis of the occluding thrombus is attempted should improve myocardial salvage. Studies of dogs by positron tomography support the hypothesis that earlier removal of the intracoronary thrombus results in greater improvement of myocardial metabolism.[7]

The potential clinical benefit of early thrombolytic treatment was evident in the results of the Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico which showed that those treated with streptokinase within the first hour of the onset of symptoms had the greatest reduction in mortality[8] and in the experience with early administration of streptokinase in Jerusalem where patients treated within one and a half hours after the onset of pain had a significantly higher ejection fraction than those treated between one and a half and four hours after the onset of pain.[9] However, neither of these studies was a controlled comparison of early and late treatment—that is the patient population treated early and those treated later may not have been comparable in terms of other treatments, for example time to

Table 5   *Mean global and infarct related regional third ejection fractions as assessed by radionuclide ventriculography*

|  | Group 1 | Group 2 |
|---|---|---|
| Mean time of scan (days) | 12·5 | 12·0 |
| GEF (all grades) (%) | 41 (n = 16) | 35 (n = 13) |
| IR RTEF (all grades) (%) | 41 | 28* |
| IR RTEF (2 and 3 reperfusion) (%) | 42 | 32 |
| IR RTEF (0 and 1 reperfusion) (%) | 26 | 24 |

*p < 0·05.
GEF, global ejection fraction; IR RTEF, infarct related regional third ejection fraction.

administration of analgesia or oxygen, or to treatment of arrhythmias, or cardiac failure.

In this placebo controlled study we have shown that it is feasible to start thrombolytic treatment with rt-PA outside hospital or in the accident and emergency department. The procedure is safe and significantly reduces the delay in starting thrombolytic treatment. A mean of 68 minutes was saved when rt-PA treatment was started once the diagnosis of myocardial infarction was suspected rather than when the patient was admitted to the coronary care unit. The patient's delay in seeking help caused the greatest delay; transit of the mobile coronary care unit team and the diagnosis of acute infarction and pain relief after arrival of the team with the patient caused less delay.

There were no complications attributable to thrombolytic treatment before admission to hospital. All seven (12%) patients who developed ventricular fibrillation during rt-PA treatment were successfully resuscitated. Ventricular fibrillation was no more common during rt-PA treatment than in an earlier study of acute myocardial infarction without thrombolysis.[10] Concern about arrhythmias during thrombolysis should not preclude rt-PA treatment before admission to hospital provided basic monitoring and resuscitation equipment are available. In most patients reperfusion is usually gradual and therefore less likely to be associated with ventricular fibrillation. Only three episodes of ventricular fibrillation occurred after the initial infusion, one on day 2, one on day 5, and one on day 7 during reinfarction.

Although the trend was towards higher reperfusion rates in those treated early (79% *v* 64%) the difference was not significant. We have already shown that reperfusion rates were improved when rt-PA treatment was started early.[1] It may be that the difference of 68 minutes to the start of rt-PA infusion between these two groups of patients did not significantly affect the reperfusion rate in group 2. rt-PA infusion was started 187 minutes after infarction in group 2 and we know that the angiographically proven reperfusion rate was 82% in patients treated with 100 mg of rt-PA over 90 minutes who were seen within four hours of the onset of acute myocardial infarction.[1] The assessment of reperfusion by angiography at 10–14 days is less accurate than immediate angiography because silent reocclusion or spontaneous reperfusion can occur in the interim. Our patients were catheterised at 10–14 days to allow left ventricular function to be assessed by contrast ventriculography.

Early treatment did not significantly improve mean global left ventricular ejection fraction (tables 3 and 5). However, the infarct related regional third ejection fraction was significantly better in group 1 than in group 2 (41% *v* 28%, p < 0.05) (table 5) and the improvement in infarct related regional wall movement was almost statistically significant (16.0 (2.7)% *v* 10.3 (2.56)%) (p = 0.06) (table 4).

In group 1 there were 13 patients with anterior infarction and 14 with inferior infarction and in group 2, 18 patients with anterior infarction, 11 with inferior infarction, and one with lateral infarction. In patients with anterior infarction the regional wall movement was significantly improved by early treatment (20.5 (2.99)% *v* 12.2 (2.23)% (p = 0.01)). Global ejection fraction is a crude estimate of left ventricular function in patients with infarction because it may be reduced by previous infarction, because hyperkinesis in a non-infarct zone may compensate for hypokinesis in the infarct area, and because return towards normal of this compensatory hyperkinesis may mask thrombolytically induced improvement in the infarct area. This may account for the improvement in left ventricular function in the infarct area without apparent significant improvement in the overall left ventricular ejection fraction as shown by both radionuclide and contrast ventriculography. Left ventricular ejection fraction and regional wall movement were no better in patients with inferior infarction who were treated earlier; nevertheless we believe that thrombolysis should be started as early as possible in patients with inferior infarction because a patent circumflex or right coronary artery may be an important source of collaterals to the anterior surface of the myocardium in patients with previous or future anterior infarction.

The improvement in infarct size with earlier treatment and as assessed by QRS scoring accorded with previous studies of early thrombolytic treatment.[9] Although QRS scoring is a crude estimate of infarct size it correlates well with left ventricular function[4] and is an easily applicable measure of myocardial salvage.

We have shown that thrombolytic treatment can be started safely by medical staff on a mobile coronary care unit; but this is not the only approach to thrombolytic treatment before admission to hospital. In areas where there are no mobile coronary care units with medical staff thrombolysis could be given by general practitioners or suitably trained paramedical personnel with adequate medical supervision probably by telephone. Infusion of rt-PA before hospital admission appreciably reduced the delay in starting thrombolysis. Earlier treatment improved myocardial function in the infarct related area and reduced infarct size. Our results confirm the advantages of reducing the delay before thrombolytic treatment.

## References

1 McNeill AJ, Shannon JS, Cunningham SR, *et al.* A randomised dose ranging study of recombinant tissue plasminogen activator in acute myocardial infarction. *Br Med J* 1988;296:1768–71.
2 National Heart Foundation of Australia Coronary Thrombolysis Group. Coronary thrombolysis and myocardial salvage by tissue plasminogen activator given up to 4 hours after the onset of myocardial infarction. *Lancet* 1988;i:203–8.
3 Lie JT, Pairolero PC, Holley KE, McCall JT, Thompson HK Jr, Titus JL. Time course and zonal variations of ischaemia-induced myocardial cationic electrolyte derangements. *Circulation* 1975;51:860–6.
4 Palmeri ST, Harrison DG, Cobb FR, *et al.* A QRS scoring system for assessing left ventricular function after myocardial infarction. *N Engl J Med* 1982;**306**:4–9.
5 Leighton RF, Wilt SM, Lewis RP. Detection of hypokinesis by a quantitative analysis of left ventricular cineangiograms. *Circulation* 1974;**50**:121–7.
6 The TIMI study group. The thrombolysis in myocardial infarction (TIMI) trial. Phase 1 findings. *N Engl J Med* 1985;312:932–6.
7 Bergmann SR, Lerch RA, Fox KAA, *et al.* Temporal dependence of beneficial effects of coronary thrombolysis characterized by positron tomography. *Am J Med* 1982;73:573–81.
8 GISSI Study Group. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;i:397–401.
9 Koren G, Weiss AT, Hasin Y, *et al.* Prevention of myocardial damage in acute myocardial ischaemia by early treatment with intravenous streptokinase. *N Engl J Med* 1985;313:1384–9.
10 Pantridge JF, Webb SW, Adgey AAJ, Geddes JS. The first hour after the onset of acute myocardial infarction. In: Yu PN, Goodwin JF, eds. *Progress in cardiology vol III*. Philadelphia: Lea and Febiger, 1974:173.